IQWiG Reports – Commission No. A19-39

Dacomitinib (non-small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dacomitinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
Del19	mutation in the EGFR gene; exon 19 deletion
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IASLC	International Association for the Study of Lung Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
L858R	mutation in the EGFR gene; exon 21 substitution of arginine for leucine
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non-small cell lung cancer
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
UICC	Union for International Cancer Control
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dacomitinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 April 2019.

Research question

The aim of the present report is the assessment of the added benefit of dacomitinib for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations in comparison with the appropriate comparator therapy (ACT).

Depending on the type of the EGFR mutation, the G-BA specified different ACTs, resulting in 2 research questions. These are presented in Table 2.

Table 2: Research questions of the benefit assessment of dacomitinib

Research question	Subindication	ACT[a]
1	Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19	Afatinib or **gefitinib** or erlotinib
2	Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or Del19	Individual treatment depending on the activating EGFR mutation, choosing from: ▪ afatinib, gefitinib, erlotinib ▪ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[b] ▪ carboplatin in combination with nab-paclitaxel and ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Prescribable despite unapproved therapeutic indication; see Appendix VI to Section K of the Pharmaceutical Directive.
ACT: appropriate comparator therapy; Del19: exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; L858R: substitution in exon 21; NSCLC: non-small cell lung cancer

It was assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to the International Association for the Study of Lung Cancer [IASLC], Union for International Cancer Control [UICC]), without medical indication for curative resection, radiotherapy or radiochemotherapy.

In the present assessment, the following terms are used for the respective populations of the research questions:

- Research question 1: patients with the activating EGFR mutations exon 21 substitution (L858R) or exon 19 deletion (Del19)
- Research question 2: patients with other activating EGFR mutations

The company followed the specification of the G-BA for research question 1 and chose gefitinib as ACT. It did not cite an ACT for research question 2 and also presented no data.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Research question 1 (patients with the activating EGFR mutations L858R or Del19)

Study pool and study characteristics

The ARCHER 1050 study was included for the assessment of the added benefit. This was an open-label RCT with gefitinib as comparator therapy. It included adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19. It was acceptable for patients with the additional presence of the exon 20 T790M mutation to be included in the study. The patients had to have a minimum of 12 months disease-free interval since completion of prior systemic therapy or a de novo diagnosis of the advanced stage. The study was stratified by the criteria of race (Japanese versus mainland Chinese versus other East Asian versus non-Asian) and EGFR mutation status (Del19 versus L858R). The study was mainly conducted in Asia.

Treatment with dacomitinib or gefitinib was to be administered for 48 months. It was largely provided as recommended in the Summaries of Product Characteristics (SPCs) of the 2 drugs.

Primary outcome was progression-free survival (PFS); secondary outcomes included overall survival, morbidity (symptoms, health status), health-related quality of life and side effects, among others.

Two data cut-offs are available for the study. A predefined analysis of PFS was conducted at a first data cut-off on 29 July 2016. The final analysis of overall survival was conducted at the second data cut-off on 17 February 2017. The company presented results on all patient-relevant outcomes for this data cut-off. It therefore formed the basis for the present benefit assessment.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes was rated as low for the ARCHER 1050 study; the outcome-specific risk of bias for the results of all outcomes except overall survival was rated as high.

On the one hand, this was due to the lack of blinding, on the other, to the possible differences in observation periods between the study arms. In addition, there were incomplete observations, which might be informative, i. e. not independent from the treatment group, for some outcomes.

Results

Mortality – overall survival

A statistically significant difference in favour of dacomitinib was shown for the outcome "overall survival". This resulted in an indication of an added benefit of dacomitinib in comparison with gefitinib.

Morbidity – symptoms

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13). In each case, the time until the single confirmed deterioration (deterioration versus baseline on at least 2 consecutive visits by ≥ 10 points) is considered.

Pain, appetite loss, diarrhoea, sore mouth, dysphagia, peripheral neuropathy, alopecia, other pain

A statistically significant difference to the disadvantage of dacomitinib was shown for the scales of pain, appetite loss, diarrhoea, sore mouth, dysphagia, peripheral neuropathy, alopecia and other pain.

This effect was no more than marginal for the outcomes "pain" and "other pain", however. This resulted in no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven for these 2 outcomes.

There was a hint of lesser benefit of dacomitinib in comparison with gefitinib for the following outcomes: appetite loss, diarrhoea, sore mouth, dysphagia, peripheral neuropathy and alopecia.

Fatigue, nausea/vomiting, dyspnoea, insomnia, constipation, cough, haemoptysis, chest pain, pain in arm/shoulder

No statistically significant difference between the treatment groups was shown for the scales of fatigue, nausea/vomiting, dyspnoea, insomnia, constipation, cough, haemoptysis, chest pain, and pain in arm/shoulder. This resulted in no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven for any of these outcomes.

Morbidity – health status

Health status was measured with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). There was no statistically significant difference between the treatment groups for the outcome "health status". Hence, there was no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales of the disease-specific instrument EORTC QLQ-C30. In each case, the time until the single confirmed deterioration (deterioration versus baseline on at least 2 consecutive visits by ≥ 10 points) is considered.

Global health status, role functioning, cognitive functioning, social functioning

A statistically significant difference to the disadvantage of dacomitinib was shown for the scales of global health status, role functioning, cognitive functioning, and social functioning. In each case, this resulted in a hint of lesser benefit of dacomitinib in comparison with gefitinib.

Physical functioning, emotional functioning

No statistically significant difference between the treatment arms was shown for the scales of physical functioning and emotional functioning. Hence, there was no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven.

Side effects

Overall rate of serious adverse events

No statistically significant difference between the treatment groups was shown for the overall rate of serious adverse events (SAEs). This resulted in no hint of greater or lesser harm from dacomitinib in comparison with gefitinib; greater or lesser harm is therefore not proven.

Overall rate of severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of dacomitinib was shown for the overall rate of severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). This resulted in a hint of greater harm from dacomitinib in comparison with gefitinib.

Overall rate of discontinuations due to adverse events

No statistically significant difference between the treatment groups was shown for the overall rate of discontinuations due to AEs. This resulted in no hint of greater or lesser harm from dacomitinib in comparison with gefitinib; greater or lesser harm is therefore not proven.

Specific adverse events with statistically significant differences between the treatment groups to the disadvantage of dacomitinib

- diarrhoea (Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term [PT], severe AEs with CTCAE grade ≥ 3)
- stomatitis (PT, AEs)
- skin and subcutaneous tissue disorders (MedDRA System Organ Class [SOC], severe AEs with CTCAE grade ≥ 3), including in particular dermatitis acneiform (PT, severe AEs with CTCAE grade ≥ 3)
- dry skin (PT, AEs)
- alopecia (PT, AEs)
- paronychia (PT, severe AEs with CTCAE grade ≥ 3)
- conjunctivitis (PT, AEs)
- eye disorders (SOC, AEs)

There was a hint of greater harm from dacomitinib in comparison with gefitinib for each of these outcomes. Due to the size of the effect, an indication of greater harm was derived for the outcome “skin and subcutaneous tissue disorders” (SOC, severe AEs with CTCAE grade ≥ 3).

Specific adverse events with statistically significant differences between the treatment arms in favour of dacomitinib

- investigations (SOC, severe AEs with CTCAE grade ≥ 3), including in particular PT alanine aminotransferase increased (severe AEs with CTCAE grade ≥ 3)
- back pain (PT, AEs)

There was lesser harm from dacomitinib in comparison with gefitinib for each of these outcomes.

Specific adverse events with statistically significant differences between the treatment arms, but with a no more than marginal effect

- chest pain (PT, AEs)
- respiratory, thoracic and mediastinal disorders (SOC, AEs)
- metabolism and nutrition disorders (SOC, AEs)

A statistically significant difference between the treatment groups was shown for these outcomes. The effect was in favour of dacomitinib for the outcome "chest pain" and to the disadvantage of dacomitinib for each of the outcomes "respiratory, thoracic and mediastinal disorders" and "metabolism and nutrition disorders". The effects were no more than marginal, however. Hence, for these outcomes, there was no hint of greater or lesser harm from dacomitinib in comparison with gefitinib; greater or lesser harm is therefore not proven.

Research question 2 (patients with other activating EGFR mutations)

The company presented no study on the added benefit of dacomitinib in adult patients with advanced or metastatic NSCLC with activating EGFR mutations other than L858R and Del19. This resulted in no hint of an added benefit of dacomitinib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug dacomitinib in comparison with the ACT are assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Both positive and negative effects of dacomitinib in comparison with gefitinib were shown for patients with the activating EGFR mutations L858R or Del19. An indication of minor added benefit was shown for the outcome "overall survival", in addition to which there were individual hints of lesser harm in severe and non-serious/non-severe side effects. On the other hand, there were numerous hints of lesser benefit or greater harm in several outcome categories, some of which of major extent.

The negative effects of dacomitinib were shown, on the one hand, in numerous side effects, particularly in severe AEs of CTCAE grade 3 and higher, and, on the other, also in earlier and/or more frequent deteriorations in patient-reported symptoms and health-related quality of life.

Overall, the large number and the large extent of the disadvantages of dacomitinib lead to the assessment that, despite mostly higher certainty of results, the positive effect for the outcome "overall survival" is outweighed by the negative effects.

The company presented no data for patients with other activating EGFR mutations. This resulted in no hint of an added benefit of dacomitinib in comparison with the ACT; an added benefit is therefore not proven.

Table 3 shows a summary of probability and extent of the added benefit of dacomitinib.

Table 3: Dacomitinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19	Afatinib or **gefitinib** or erlotinib	Added benefit not proven[b]
Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or Del19	Individual treatment depending on the activating EGFR mutation, choosing from: ▪ afatinib, gefitinib, erlotinib ▪ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[c] ▪ carboplatin in combination with nab-paclitaxel and ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The ARCHER 1050 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
c: Prescribable despite unapproved therapeutic indication; see Appendix VI to Section K of the Pharmaceutical Directive.
ACT: appropriate comparator therapy; Del19: exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; L858R: substitution in exon 21; NSCLC: non-small cell lung cancer

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of dacomitinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR-activating mutations in comparison with the ACT.

Depending on the type of the EGFR mutation, the G-BA specified different ACTs. These resulted in 2 research questions, which are presented in Table 4.

Table 4: Research questions of the benefit assessment of dacomitinib

Research question	Subindication	ACT[a]
1	Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19	Afatinib or **gefitinib** or erlotinib
2	Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or Del19	Individual treatment depending on the activating EGFR mutation, choosing from: ▪ afatinib, gefitinib, erlotinib ▪ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[b] ▪ carboplatin in combination with nab-paclitaxel and ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Prescribable despite unapproved therapeutic indication; see Appendix VI to Section K of the Pharmaceutical Directive.
ACT: appropriate comparator therapy; Del19: exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; L858R: substitution in exon 21; NSCLC: non-small cell lung cancer

It was assumed for the present therapeutic indication that the NSCLC patients have stage IIIB to IV disease (staging according to the IASLC, UICC), without medical indication for curative resection, radiotherapy or radiochemotherapy.

In the present assessment, the following terms are used for the respective populations of the research questions:

- Research question 1: patients with the activating EGFR mutations exon 21 substitution (L858R) or exon 19 deletion (Del19)
- Research question 2: patients with other activating EGFR mutations

The company followed the specification of the G-BA for research question 1 and chose gefitinib as ACT. It did not cite an ACT for research question 2 and also presented no data.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 Research question 1: patients with the activating EGFR mutations L858R or Del19

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dacomitinib (status: 20 March 2019)
- bibliographical literature search on dacomitinib (last search on 20 March 2019)
- search in trial registries for studies on dacomitinib (last search on 20 March 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dacomitinib (last search on 13 May 2019)

The check identified no additional relevant study.

2.3.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dacomitinib vs. gefitinib

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ARCHER 1050	Yes	Yes	Yes
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

The study pool concurred with that of the company.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: dacomitinib vs. gefitinib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARCHER 1050	RCT, open-label, parallel	Adult patients (≥ 18 years [≥ 20 years in Japan/Republic of Korea]) ▪ with locally advanced or metastatic NSCLC (stage IIIB/IV) ▪ with activating EGFR mutation (Del19 or L858R in exon 21)[b] ▪ who are treatment-naive for the advanced disease stage, and ▪ who had a minimum of 12 months interval since completion of (neo)adjuvant therapy ▪ ECOG PS 0 or 1	Dacomitinib (N = 227) gefitinib (N = 225[c])	▪ Screening: until 28 days before start of treatment ▪ Treatment: in 28-day cycles for up to 48 months or until occurrence of one of the following criteria: disease progression, initiation of new cancer treatment, unacceptable toxicity, global deterioration of health status, pregnancy, withdrawal of consent, loss to follow-up, death, at the investigator's decision, termination of study by the sponsor[d, e] ▪ Observation[f]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	90 centres in China, Hong Kong, Italy, Japan, Poland, Republic of Korea, Spain 5/2013–ongoing First data cut-off: 29 July 2016 Second data cut-off: 17 Feb 2017	Primary: progression-free survival Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the study included – RCT, direct comparison: dacomitinib vs. gefitinib (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: The EGFR mutation status was determined using standardized commercial test kits (Qiagen therascreen EGFR Mutation Detection Kit RGQ [FDA-approved companion diagnostic]; Amoy Dx EGFR Mutations Detection Kit, Cobas EGFR Mutation Test, Panagene PNA Clamp); in China only therascreen and Amoy Dx Kits were used.
c: One patient in the gefitinib arm received no study medication.
d: In individual cases, treatment with the study medication could be continued even in the case of disease progression, provided the investigator deemed this to be in the patient's interest.
e: Patients without disease progression after 48 months could continue treatment with dacomitinib or gefitinib at the discretion of the investigator.
f: Outcome-specific information is provided in Table 8.

AE: adverse event; Del19: exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; FDA: Food and Drug Administration; L858R: substitution in exon 21; N: number of randomized patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: dacomitinib vs. gefitinib

Study	Intervention	Comparison
ARCHER 1050	Dacomitinib 45 mg once daily, orally, together with at least 180 mL water	Gefitinib 250 mg once daily, orally
	▪ Dose reduction in 2 steps (30 mg and 15 mg, once daily) possible in case of treatment-related toxicity: ▫ the dose could subsequently be increased again ▫ treatment discontinuation if 15 mg was not tolerated ▪ Treatment interruption possible in case of severe AEs: ▫ possible re-initiation of treatment at the same or a reduced dose ▫ treatment discontinuation in case of interruption due to treatment-related toxicity > 2 weeks	▪ Dose reduction possible after treatment interruption in case of treatment-related toxicity and severe AEs: ▫ possible re-initiation of treatment with temporarily reduced frequency (every second day); if possible, treatment should be switched again to once daily dosing ▫ treatment discontinuation in case of interruption due to treatment-related toxicity > 2 weeks
	Pretreatment ▪ Any previous anti-cancer systemic treatment of locally advanced or metastatic NSCLC was prohibited. ▪ (Neo)adjuvant pretreatment of NSCLC was allowed if there was a minimum of 12 months interval between completion of treatment and recurrence.	
	Concomitant treatment ▪ CYP2D6-dependent drugs: with narrow therapeutic indices prohibited in the dacomitinib arm (also between screening and randomization); use of further CYP2D6 substrates under close clinical monitoring, provided that it is not possible to switch to other drugs. ▪ Lidocaine and P-glycoprotein substrates with narrow therapeutic indices should only be administered under close clinical monitoring. ▪ Proton pump inhibitors and H_2 receptor antagonists should be avoided as far as possible. The use of short-acting antacids was allowed. ▪ Bisphosphonates, denosumab and other drugs to control bone metastases that were already present before baseline could be continued (use in lesions that occurred later was considered disease progression). ▪ Palliative radiotherapy was allowed if painful bone lesions were present at baseline and was considered to be better for pain relief than other measures.	

AE: adverse event; CYP2D6: cytochrome P450 isoenzyme 2D6; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

The ARCHER 1050 study was an open-label RCT with gefitinib as comparator therapy. It included adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19. It was acceptable for patients with the additional presence of the exon 20 T790M mutation to be included in the study. The patients had to have a minimum of 12 months disease-free interval since completion of prior systemic therapy or a de novo diagnosis of the advanced stage. The study was stratified by the criteria of race (Japanese versus

mainland Chinese versus other East Asian versus non-Asian) and EGFR mutation status (Del19 versus L858R). The study was mainly conducted in Asia.

Treatment with the study medications was largely provided as recommended in the SPCs [3,4]. Treatment in the gefitinib arm could be interrupted if severe AEs occurred, followed by continued treatment with a temporarily reduced dose (every second day instead of daily). The SPC does not provide for a dose reduction in this way. According to information provided in the clinical study report (CSR), a total of 18 patients (8.0%) were treated with such a reduced dosage up to the first data cut-off (see below). Treatment was interrupted in 26.8% of the patients in the gefitinib arm. In the dacomitinib arm, dose reductions (single or permanent) occurred in 66.1% of the patients and at least 1 treatment interruption in 78.0%. The company provided no information on the current data cut-off.

Treatment with dacomitinib or gefitinib was to be administered for 48 months. Patients who had not had disease progression until then could continue treatment beyond this period at the discretion of the investigators. On occurrence of progression, treatment was to be discontinued or subsequent therapy initiated. In individual cases, treatment with the study medication could be continued even in the case of disease progression, provided the investigator deemed this to be in the patient's interest.

Switching between study medications on disease progression was not allowed. The study had no limitations regarding the administration of subsequent cancer treatments.

Primary outcome was PFS; secondary outcomes included overall survival, morbidity (symptoms, health status), health-related quality of life and side effects, among others.

Two data cut-offs are available for the study. A predefined analysis of PFS was conducted at a first data cut-off on 29 July 2016. The final analysis of overall survival was conducted at the second data cut-off on 17 February 2017. The company presented results on all patient-relevant outcomes for this data cut-off. It therefore formed the basis for the present benefit assessment.

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: dacomitinib vs. gefitinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ARCHER 1050	
Mortality	
Overall survival	▪ After discontinuation of treatment every 2 months until death (at most up to 48 months after the first dose of the study medication)
Morbidity	
Symptoms (EORTC QLQ-C30 [symptom scales] and EORTC QLQ-LC13; health status [EQ-5D VAS])	▪ Until the last follow-up visit (28 to 35 days after the last dose of the study medication)
Health-related quality of life (EORTC QLQ-C30, functional scales)	▪ Until the last follow-up visit (28 to 35 days after the last dose of the study medication)
Side effects	
All outcomes in the category "side effects"	▪ AEs: until the start of a new cancer treatment, but at most until 28 to 35 days after the last dose of the study medication[a] ▪ SAEs: until 28 days after the last dose of the study medication[a]
a: According to the study documents, it was also possible to include AEs that were reported at a later time point. It cannot be inferred from the company's data whether this recording was carried out systematically for all events and in how many patients this was the case.	
AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus	

The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because, in accordance with the study plan, they were only recorded for the time period of treatment with the study medication (plus 28 to 35 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study **Characteristics** **Category**	**Dacomitinib**	**Gefitinib**
ARCHER 1050	N[a] = 227	N[a] = 225
Age [years], mean (SD)	61 (11)	61 (10)
Sex [F/M], %	64/36	56/44
Region, n (%)		
Asia (China, Hong Kong, Japan, Republic of Korea)	170 (74.9)[b]	175 (77.8)[b]
Europe (Italy, Poland, Spain)	57 (25.1)[b]	50 (22.3)[b]
Smoking status, n (%)		
Never smoker	147 (64.8)	144 (64.0)
Ex-smoker	65 (28.6)	62 (27.6)
Smoker	15 (6.6)	19 (8.4)
ECOG PS, n (%)		
0	75 (33.0)	62 (27.6)
1	152 (67.0)	163 (72.4)
Histology, n (%)		
Adenocarcinoma	227 (100)	225 (100)
Current disease stage, n (%)		
IIIB	18 (7.9)	16 (7.1)
IV	184 (81.1)	183 (81.3)
Unknown[c]	25 (11.0)	26 (11.6)
Most common location of disease		
Bone	51 (22.5)	81 (36.0)
Liver	21 (9.3)	33 (14.7)
Left lung, below	59 (26.0)	55 (24.4)
Right lung, below	62 (27.3)	71 (31.6)
Left lung, above	62 (27.3)	50 (22.2)
Right lung, above	82 (36.1)	86 (38.2)
Lymph nodes, hilar	56 (24.7)	59 (26.2)
Lymph nodes, mediastinal	117 (51.5)	128 (56.9)
Pleura	50 (22.0)	59 (26.2)
EGFR mutation at start of treatment, n (%)		
L858R mutation in exon 21	93 (41.0)	92 (40.9)
With T790M mutation	2 (0.9)	0 (0.0)
Exon 19 deletion	134 (59.0)	133 (59.1)
With T790M mutation	0 (0.0)	2 (0.9)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Study **Characteristics** **Category**	**Dacomitinib**	**Gefitinib**
ARCHER 1050	N[a] = 227	N[a] = 225
Prior cancer treatment		
Surgical intervention	21 (9.3)	19 (8.4)
Radiotherapy	7 (3.1)	6 (2.7)
Systemic therapy	2 (0.9)	2 (0.9)
Platinum-based therapy	2 (0.9)	2 (0.9)
Number of treatment regimens	2 (0.9)	2 (0.9)
0	0 (0.0)	0 (0.0)
1	2 (0.9)	2 (0.9)
≥ 2	0 (0.0)	0 (0.0)
Treatment discontinuation	178 (78.4)	206 (91.6)
Study discontinuation	125 (55.1)[d]	140 (62.2)[d]

a: Number of randomized patients.
b: Institute's calculation.
c: According to the company, all patients with unknown status were newly diagnosed with stage IV on study entry (< 2 months interval from the initial stage of disease, which probably means the time since the initial diagnosis) and were confirmed after the data cut-off.
d: The main reason for study discontinuation in both treatment groups was death of the patient (45.4% deaths in the dacomitinib arm and 52.0% in the gefitinib arm).
Del19: exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status;
EGFR: epidermal growth factor receptor; L858R: substitution in exon 21; n: number of patients in the category;
N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The distribution of the patient characteristics was largely comparable between the study arms. The mean age of the patients was 61 years, and all of them were in good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0 or 1). Women were in the majority in the study (about 60% versus 40% of the population). The proportion of non-smokers, i.e. people who have never smoked, was 64%.

About 3 quarters of the population were from Asia, where most study centres were located. In Europe, the study was conducted in centres in Italy, Poland and Spain.

The majority of the patients (at least 81%) had a metastatic disease stage at the start of the study. Noteworthy is the high proportion of study participants with unclear diagnosis at the start of the study (11%), which, according to the company, were patients with de novo diagnosis in stage IV.

All study participants had either L858R or Del19 mutation. T790 mutation in the EGFR exon 20, which can lead to resistance to treatment with tyrosine kinase inhibitors [5,6], was not a general exclusion criterion. Only few patients had this mutation, however (< 1%).

Treatment discontinuations were more common in patients in the gefitinib arm. More than half of the participants discontinued the study prematurely. Almost 50% of the study participants in the dacomitinib arm and 62% in the gefitinib arm received subsequent therapy, with cisplatin, pemetrexed, carboplatin and osimertinib being the most commonly administered subsequent therapies (see Appendix C of the full dossier assessment). Erlotinib (6.2% in the dacomitinib arm versus 8.9% in the gefitinib arm) and gefitinib (7.9% versus 7.1%) were also used in the following lines of treatment.

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Characteristics on the course of the study – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study **Duration of the study phase** **Outcome category**	**Dacomitinib**	**Gefitinib**
ARCHER 1050	N = 227	N = 224
Treatment duration [months]		
Median [min; max]	15.3 [0.1; 44.1]	12.0 [0.1; 40.8]
Observation period [months]		
Overall survival		
Median [min; max]	26.2 [0.4; 44.1]	24.4 [0.9; 45.2]
Morbidity (EORTC QLQ-C30 and QLQ-LC13; EQ-5D VAS) and health related quality of life (EORTC QLQ-C30)		
Median [min; max]	ND[a]	ND[a]
Side effects		
Median [min; max]	ND[a]	ND[a]

a: According to the study protocol, the scales on symptoms and health-related quality of life were recorded until the follow-up visit (28 to 35 days after the end of treatment visit).

Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; L858R: substitution in exon 21; max.: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The company's documents contain no information on the observation period of the patient-relevant outcomes except overall survival on the present data cut-off. For all these outcomes, the observation period was linked to the duration of treatment. This was 25% longer in the dacomitinib arm than in the gefitinib arm. Hence, a possibly relevant difference in observation periods was assumed for the present assessment.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ARCHER 1050	Yes	Yes	No	No	Yes	Yes	Low

Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; L858R: substitution in exon 21; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the ARCHER 1050 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.3.2.2.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the symptom scales of the EORTC QLQ-C30 and of the EORTC QLQ-LC13
  - health status, measured using the EQ-5D VAS
- Health-related quality of life
  - EORTC QLQ-C30 (functional scales)
- Side effects
  - overall rate of SAEs
  - overall rate of severe AEs (CTCAE grade ≥ 3)

- overall rate of discontinuations due to AEs
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.4.3.2 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study	Outcomes							
	Overall survival	Symptoms (EORTC QLQ-C30 [symptom scales]; EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 functional scales)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Further specific AEs[a]
ARCHER 1050	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: The following events (MedDRA coding) are considered: “diarrhoea (PT, severe AEs with CTCAE grade ≥ 3)”, “stomatitis (PT, AEs)”, “skin and subcutaneous tissue disorders (SOC, severe AEs with CTCAE grade ≥ 3)”, “dry skin (PT, AEs)”, “alopecia (PT, AEs)”, “chest pain (PT, AEs)”, “paronychia (PT, severe AEs with CTCAE grade ≥ 3)”, “conjunctivitis (PT, AEs)”, “respiratory, thoracic and mediastinal disorders (SOC, AEs)”, “metabolism and nutrition disorders (SOC, AEs)”, “back pain (PT, AEs)”, “eye disorders (SOC, AEs)”, “investigations (SOC, severe AEs with CTCAE grade ≥ 3)”.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; L858R: substitution in exon 21; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study		Outcomes							
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 [symptom scales]; EORTC QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, functional scales)	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs	Further specific AEs[c]
ARCHER 1050	L	L	H[a, b]	H[a, b]	H[a, b]	H[b]	H[b]	H[a]	H[a, b]

a: Lack of blinding in subjective recording of outcomes.
b: Incomplete observations for potentially informative reasons, presumably differences in the observation periods between the treatment groups.
c: The following events (MedDRA coding) are considered: "diarrhoea (PT, severe AEs with CTCAE grade ≥ 3)", "stomatitis (PT, AEs)", "skin and subcutaneous tissue disorders (SOC, severe AEs with CTCAE grade ≥ 3)", "dry skin (PT, AEs)", "alopecia (PT, AEs)", "chest pain (PT, AEs)", "paronychia (PT, severe AEs with CTCAE grade ≥ 3)", "conjunctivitis (PT, AEs)", "respiratory, thoracic and mediastinal disorders (SOC, AEs)", "metabolism and nutrition disorders (SOC, AEs)", "back pain (PT, AEs)", "eye disorders (SOC, AEs)", "investigations (SOC, severe AEs with CTCAE grade ≥ 3)".

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; L858R: substitution in exon 21; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The outcome-specific risk of bias was rated as high for the results of all outcomes except overall survival. This concurs with the company's assessment.

On the one hand, this was due to the lack of blinding, on the other, to the presumed differences in observation periods between the study arms. In addition, there were incomplete observations, which might be informative for some outcomes.

2.3.2.3 Results

Table 14 and Table 15 summarize the results of the comparison of dacomitinib with gefitinib in adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves for all included

outcomes with event time analyses can be found in Appendix B of the full dossier assessment. Common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs are listed in Appendix A of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study Outcome category Outcome	Dacomitinib N	Dacomitinib Median time to event in months [95% CI] Patients with event n (%)	Gefitinib N	Gefitinib Median time to event in months [95% CI] Patients with event n (%)	Dacomitinib vs. gefitinib HR [95% CI]; p-value[a]
ARCHER 1050					
Mortality					
Overall survival	227	34.1 [29.5; 37.7] 103 (45.5)	225	26.8 [23.7; 32.1] 117 (52.0)	0.76 [0.58; 0.99]; 0.044
Morbidity (symptoms)					
EORTC QLQ-C30 (symptom scales)[b]					
Fatigue	226	29.0 [15.0; NC] 92 (40.7)	222	NA [20.8; NC] 75 (33.8)	1.30 [0.95; 1.76]; 0.090
Nausea/vomiting	226	NA 50 (22.1)	222	NA 35 (15.8)	1.44 [0.93; 2.22]; 0.099
Pain	226	33.7 [17.7; NC] 87 (38.5)	222	NA [24.9; NC] 68 (30.6)	1.40 [1.02; 1.93]; 0.036
Dyspnoea	226	NA 50 (22.1)	222	NA 44 (19.8)	1.03 [0.68; 1.55]; 0.897
Insomnia	226	NA 51 (22.6)	222	NA 46 (20.7)	1.09 [0.73; 1.63]; 0.662
Appetite loss	226	NA [17.7; NC] 87 (38.5)	222	NA 60 (27.0)	1.61 [1.16; 2.24]; 0.004
Constipation	226	NA [39.4; NC] 35 (15.5)	222	NA 38 (17.1)	0.82 [0.51; 1.30]; 0.393
Diarrhoea	226	0.5 [0.3; 0.5] 179 (79.2)	222	40.2 [12.1; 40.2] 93 (41.9)	3.45 [2.65; 4.49]; < 0.001
EORTC QLQ-LC13[b]					
Dyspnoea	226	40.2 [40.2; NC] 75 (33.2)	222	NA [20.8; NC] 74 (33.3)	0.99 [0.72; 1.37]; 0.957
Cough	226	NA 30 (13.3)	222	NA 33 (14.9)	0.86 [0.52; 1.41]; 0.538
Haemoptysis	226	NA 13 (5.8)	222	NA 16 (7.2)	0.77 [0.37; 1.61]; 0.485
Sore mouth	226	0.5 [0.5; 1.0] 155 (68.6)	222	NA 73 (32.9)	3.27 [2.45; 4.35]; < 0.001

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Study Outcome category	Dacomitinib		Gefitinib		Dacomitinib vs. gefitinib
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Dysphagia	226	NA 69 (30.5)	222	NA 32 (14.4)	2.47 [1.62; 3.77]; < 0.001
Neuropathy peripheral	226	6.3 [4.6; 12.3] 120 (53.1)	222	NA 56 (25.2)	2.84 [2.06; 3.92]; < 0.001
Alopecia	226	5.6 [4.2; 10.4] 115 (50.9)	222	NA [31.7; NC] 80 (36.0)	1.68 [1.26; 2.24]; < 0.001
Chest pain	226	NA 33 (14.6)	222	NA 38 (17.1)	0.81 [0.51; 1.30]; 0.375
Pain in arm/shoulder	226	NA [34.6; NC] 45 (19.9)	222	NA 46 (20.7)	0.90 [0.59; 1.36]; 0.612
Other pain	226	NA 70 (31.0)	222	NA 45 (20.3)	1.61 [1.11; 2.35]; 0.012
Health-related quality of life					
EORTC QLQ-C30 (functional scales)[c]					
Global health status	226	26.3 [17.7; NC] 92 (40.7)	222	NA 52 (23.4)	1.99 [1.41; 2.81]; < 0.001
Physical functioning	226	NA 60 (26.5)	222	NA [27.0; NC] 45 (20.3)	1.38 [0.94; 2.04]; 0.099
Role functioning	226	NA [19.5; NC] 87 (38.5)	222	NA [24.9; NC] 64 (28.8)	1.48 [1.07; 2.05]; 0.016
Emotional functioning	226	NA 50 (22.1)	222	NA 39 (17.6)	1.29 [0.85; 1.96]; 0.236
Cognitive functioning	226	20.5 [13.1; NC] 95 (42.0)	222	NA [26.3; NC] 71 (32.0)	1.40 [1.03; 1.91]; 0.031
Social functioning	226	NA [9.4; NC] 99 (43.8)	222	NA [21.5; NC] 75 (33.8)	1.45 [1.07; 1.96]; 0.013

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Study **Outcome category** **Outcome** **Time point**	**Dacomitinib** **N**	**Dacomitinib** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Gefitinib** **N**	**Gefitinib** **Median time to event in months [95% CI]** **Patients with event n (%)**	**Dacomitinib vs. gefitinib** **HR [95% CI]; p-value[a]**
Side effects					
AEs (supplementary information)	227	ND 226 (99.6)	224	ND 220 (98.2)	-
SAEs	227	NA [30.4; NC] 66 (29.1)	224	NA [31.4; NC] 52 (23.2)	1.20 [0.84; 1.74]; 0.321
Severe AEs (CTCAE grade ≥ 3)	227	5.6 [3.9; 9.2] 146 (64.3)	224	23.5 [13.5; 31.4] 98 (43.8)	1.89 [1.46; 2.45]; < 0.001
Discontinuation due to AEs	227	NA 41 (18.1)	224	NA 29 (12.9)	1.31 [0.81; 2.11]; 0.266
Diarrhoea (PT, severe AEs with CTCAE grade ≥ 3)	227	NA 20 (8.8)	224	NA 2 (0.9)	10.22 [2.39; 43.77]; < 0.001
Stomatitis (PT, AEs)	227	NA [14.6; NC] 99 (43.6)	224	NA 41 (18.3)	3.40 [2.35; 4.92]; < 0.001
Skin and subcutaneous tissue disorders (SOC, severe AEs with CTCAE grade ≥ 3)	227	NA 66 (29.1)	224	NA 5 (2.2)	14.47 [5.82; 35.94]; < 0.001
Including: dermatitis acneiform (PT, severe AEs with CTCAE grade ≥ 3)	*227*	*NA* *31 (13.7)*	*224*	*NA* *0 (0.0)*	–[d] *< 0.001*
Dry skin (PT, AEs)	227	NA 63 (27.8)	224	NA 38 (17.0)	1.74 [1.16; 2.61]; 0.007
Alopecia (PT, AEs)	227	NA 53 (23.3)	224	NA 28 (12.8)	2.02 [1.28; 3.20]; 0.002
Chest pain (PT, AEs)	227	NA 24 (10.6)	224	NA 34 (15.2)	0.57 [0.33; 0.96]; 0.032

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Study **Outcome category**	**Dacomitinib**		**Gefitinib**		**Dacomitinib vs. gefitinib**
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Paronychia (PT, severe AEs with CTCAE grade ≥ 3)	227	NA 17 (7.5)	224	NA 3 (1.3)	5.82 [1.70; 19.87]; 0.001
Conjunctivitis (PT, AEs)	227	NA 43 (18.9)	224	NA 10 (4.5)	4.87 [2.44; 9.72]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	227	10.2 [6.7; 15.9] 124 (54.6)	224	16.3 [11.1; NC] 98 (43.8)	1.33 [1.02; 1.74]; 0.035
Metabolism and nutrition disorders (SOC, AEs)	227	15.9 [9.2; 23.9] 110 (48.5)	224	25.8 [16.8; NC] 81 (36.2)	1.45 [1.09; 1.93]; 0.011
Back pain (PT, AEs)	227	NA 18 (7.9)	224	NA 37 (16.5)	0.41 [0.23; 0.72]; 0.002
Eye disorders (SOC, AEs)	227	NA 44 (19.4)	224	NA 22 (9.8)	2.03 [1.21; 3.39]; 0.006
Investigations (SOC, severe AEs with CTCAE grade ≥ 3)	227	NA 19 (8.4)	224	NA 37 (16.5)	0.44 [0.25; 0.77]; 0.003
Including: *alanine aminotransferase increased (PT, severe AEs with CTCAE grade ≥ 3)*	*227*	*NA* *2 (0.9)*	*224*	*NA* *20 (8.9)*	*0.09 [0.02; 0.40];* *< 0.001*

a: Cox model, stratified by randomization factors, p-value from stratified log-rank test.
b: An increase in score by ≥ 10 points compared with baseline, measured in at least 2 consecutive visits, is considered as single confirmed deterioration.
c: A decrease in score by ≥ 10 points compared with baseline, measured in at least 2 consecutive visits, is considered as single confirmed deterioration.
d: Magnitude of the HR not interpretable (0 events in the gefitinib arm).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; HR: hazard ratio; L858R: substitution in exon 21; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 15: Results (morbidity, continuous) – RCT, direct comparison: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Study Outcome category	Dacomitinib			Gefitinib			Dacomitinib vs. gefitinib
Outcome	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at end of study mean[b] (SE)	MD [95% CI]; p-value[b]
ARCHER 1050							
Morbidity							
Health status							
EQ-5D VAS	224	73.05 (19.62)	0.31 (1.38)	221	74.71 (17.62)	1.19 (2.17)	−0.88 [−5.94; 4.18]; 0.733

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study may be based on other patient numbers.
b: MMRM with covariables treatment, time, baseline value and treatment x time interaction.
CI: confidence interval; Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; EQ-5D: European Quality of Life-5 Dimensions; L858R: substitution in exon 21; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome "overall survival", and initially at most a hint for the outcomes on symptoms, health status, health-related quality of life and side effects due to the high risk of bias. The outcome-specific certainty of conclusions of the results may not be downgraded, however.

Mortality

Overall survival

A statistically significant difference in favour of dacomitinib was shown for the outcome "overall survival". This resulted in an indication of an added benefit of dacomitinib in comparison with gefitinib.

This concurs with the company's assessment.

Morbidity

Symptoms, recorded with EORTC QLQ-C30 (symptom scales) and EORTC QLQ-LC13

Pain, appetite loss, diarrhoea, sore mouth, dysphagia, peripheral neuropathy, alopecia, other pain

A statistically significant difference to the disadvantage of dacomitinib was shown for the scales of pain, appetite loss, diarrhoea, sore mouth, dysphagia, peripheral neuropathy, alopecia and other pain.

This effect was no more than marginal for the outcomes “pain” and “other pain”, however. This resulted in no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven for these 2 outcomes.

There was a hint of lesser benefit of dacomitinib in comparison with gefitinib for the following outcomes: appetite loss, diarrhoea, sore mouth, dysphagia, peripheral neuropathy and alopecia.

This deviates from the assessment of the company, which considered an added benefit as not proven for all symptom scales of the EORTC QLQ-C30.

Fatigue, nausea/vomiting, dyspnoea, insomnia, constipation, cough, haemoptysis, chest pain, pain in arm/shoulder

No statistically significant difference between the treatment groups was shown for the scales of fatigue, nausea/vomiting, dyspnoea, insomnia, constipation, cough, haemoptysis, chest pain, and pain in arm/shoulder. This resulted in no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven for any of these outcomes.

This concurs with the company’s assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome “health status”. Hence, there was no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

Global health status, role functioning, cognitive functioning, social functioning

A statistically significant difference to the disadvantage of dacomitinib was shown for the scales of global health status, role functioning, cognitive functioning, and social functioning. In each case, this resulted in a hint of lesser benefit of dacomitinib in comparison with gefitinib.

This deviates from the assessment of the company, which considered an added benefit as not proven for all functional scales of the EORTC QLQ-C30.

Physical functioning, emotional functioning

No statistically significant difference between the treatment arms was shown for the scales of physical functioning and emotional functioning. Hence, there was no hint of an added benefit of dacomitinib in comparison with gefitinib; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Side effects

Overall rate of serious adverse events

No statistically significant difference between the treatment groups was shown for the overall rate of SAEs. This resulted in no hint of greater or lesser harm from dacomitinib in comparison with gefitinib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Overall rate of severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of dacomitinib was shown for the overall rate of severe AEs. This resulted in a hint of greater harm from dacomitinib in comparison with gefitinib.

This concurs with the company's assessment.

Overall rate of discontinuations due to adverse events

No statistically significant difference between the treatment groups was shown for the overall rate of discontinuations due to AEs. This resulted in no hint of greater or lesser harm from dacomitinib in comparison with gefitinib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific adverse events

There were numerous specific AEs with statistically significant differences between the treatment groups in the ARCHER 1050 study. They are described below, sorted by direction of effect and effect size.

Specific adverse events with statistically significant differences between the treatment groups to the disadvantage of dacomitinib

- diarrhoea (MedDRA PT, severe AEs with CTCAE grade ≥ 3)
- stomatitis (PT, AEs)
- skin and subcutaneous tissue disorders (MedDRA SOC, severe AEs with CTCAE grade ≥ 3), including in particular dermatitis acneiform (PT, severe AEs with CTCAE grade ≥ 3)
- dry skin (PT, AEs)
- alopecia (PT, AEs)
- paronychia (PT, severe AEs with CTCAE grade ≥ 3)
- conjunctivitis (PT, AEs)
- eye disorders (SOC, AEs)

There was a hint of greater harm from dacomitinib in comparison with gefitinib for each of these outcomes. Due to the size of the effect, an indication of greater harm was derived for the outcome "skin and subcutaneous tissue disorders" (SOC, severe AEs with CTCAE grade ≥ 3).

The company also derived greater harm for these outcomes.

Specific adverse events with statistically significant differences between the treatment arms in favour of dacomitinib

- investigations (SOC, severe AEs with CTCAE grade ≥ 3), including PT alanine aminotransferase increased (severe AEs with CTCAE grade ≥ 3)
- back pain (PT, AEs)

There was lesser harm from dacomitinib in comparison with gefitinib for each of these outcomes.

This concurs with the assessment of the company, which made no statement on the SOC investigations, since it considered the associated PTs to be too different in their genesis.

Specific adverse events with statistically significant differences between the treatment arms, but with a no more than marginal effect

- chest pain (PT, AEs)
- respiratory, thoracic and mediastinal disorders (SOC, AEs)
- metabolism and nutrition disorders (SOC, AEs)

A statistically significant difference between the treatment groups was shown for these outcomes. The effect was in favour of dacomitinib for the outcome "chest pain" and to the disadvantage of dacomitinib for each of the outcomes "respiratory, thoracic and mediastinal disorders" and "metabolism and nutrition disorders". The effects were no more than marginal, however. Hence, for these outcomes, there was no hint of greater or lesser harm from dacomitinib in comparison with gefitinib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.3.2.4 Subgroups and other effect modifiers

Subgroup results were not available for all outcomes or operationalizations included in the present assessment. This applies in particular to the patient-reported outcomes (EORTC QLQ-C30 and QLQ-LC13 as well as EQ-5D VAS). In its dossier, the company presented subgroup analyses only for its primary analysis of these outcomes, i.e. for the time to first deterioration. For the present assessment, however, the time to (first) confirmed deterioration was considered to be the more meaningful operationalization and was used for the assessment (see Section 2.6.4.3.2 of the full dossier assessment).

Since there was no proof of an effect modification for the outcome "overall survival" and subgroup analyses were missing for all outcomes on morbidity and health-related quality of life, subgroups were not considered in the framework of this benefit assessment.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 16).

Determination of the outcome category for outcomes on symptoms and side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The symptom scales of the questionnaires EORTC QLQ-C30 and QLQ-LC13 are considered as non-serious/non-severe outcomes. There is no information on absolute threshold values of the EORTC scales that mark a transition from non-severe to severe manifestation of a symptom or late complication on a scale. In addition, the data show that the values both at baseline and at the end of the study were in the lower quarters of the respective symptom scales.

For outcomes on specific side effects, preference was given to the consideration of events with severe manifestations (CTCAE grade ≥ 3). All other outcomes on specific side effects with statistically significant effects were allocated to the category of non-serious/non-severe side effects, as the events included in these outcomes were mostly non-serious/non-severe.

Table 16: Extent of added benefit at outcome level: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19)

Outcome category **Outcome**	**Dacomitinib vs. gefitinib** **Median time to event (months) or MD** **Hazard ratio [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	34.1 vs. 26.8 HR: 0.76 [0.58; 0.99] p = 0.044 probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
EORTC QLQ-C30 (symptom scales)		
Fatigue	29.0 vs. NA HR: 1.30 [0.95; 1.76] p = 0.090	Lesser benefit/added benefit not proven
Nausea/vomiting	NA vs. NA HR: 1.44 [0.93; 2.22] p = 0.099	Lesser benefit/added benefit not proven
Pain	33.7 vs. NA HR: 1.40 [1.02; 1.93] HR[c]: 0.71 [0.52; 0.98] p = 0.036	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Dyspnoea	NA vs. NA HR: 1.03 [0.68; 1.55] p = 0.897	Lesser benefit/added benefit not proven
Insomnia	NA vs. NA HR: 1.09 [0.73; 1.63] p = 0.662	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 1.61 [1.16; 2.24] HR[c]: 0.62 [0.45; 0.86] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ lesser benefit, extent: "minor"
Constipation	NA vs. NA HR: 0.82 [0.51; 1.30] p = 0.393	Lesser benefit/added benefit not proven
Diarrhoea	0.5 vs. 40.2 HR: 3.45 [2.65; 4.49] HR[c]: 0.29 [0.22; 0.38] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u \leq 0.80$ lesser benefit, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Outcome category **Outcome**	**Dacomitinib vs. gefitinib** **Median time to event (months) or MD** **Hazard ratio [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-LC13		
Dyspnoea	40.2 vs. NA HR: 0.99 [0.72; 1.37] p = 0.957	Lesser benefit/added benefit not proven
Cough	NA vs. NA HR: 0.86 [0.52; 1.41] p = 0.538	Lesser benefit/added benefit not proven
Haemoptysis	NA vs. NA HR: 0.77 [0.37; 1.61] p = 0.485	Lesser benefit/added benefit not proven
Sore mouth	0.5 vs. NA HR: 3.27 [2.45; 4.35] HR[c]: 0.31 [0.23; 0.41] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: "considerable"
Dysphagia	NA vs. NA HR: 2.47 [1.62; 3.77] HR[c]: 0.40 [0.27; 0.62] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: "considerable"
Neuropathy peripheral	6.3 vs. NA HR: 2.84 [2.06; 3.92] HR[c]: 0.35 [0.26; 0.49] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: "considerable"
Alopecia	5.6 vs. NA HR: 1.68 [1.26; 2.24] HR[c]: 0.60 [0.45; 0.79] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: "considerable"
Chest pain	NA vs. NA HR: 0.81 [0.51; 1.30] p = 0.375	Lesser benefit/added benefit not proven
Pain in arm/shoulder	NA vs. NA HR: 0.90 [0.59; 1.36] p = 0.612	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Outcome category **Outcome**	**Dacomitinib vs. gefitinib** **Median time to event (months) or MD** **Hazard ratio [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Other pain	NA vs. NA HR: 1.61 [1.11; 2.35] HR[c]: 0.62 [0.43; 0.90] p = 0.012	Outcome category: non-serious/non-severe symptoms $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Health status		
EQ-5D VAS	0.31 vs. 1.19[e] MD: −0.88 [−5.94; 4.18]; p = 0.733	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (functional scales)		
Global health status	26.3 vs. NA HR: 1.99 [1.41; 2.81] HR[c]: 0.50 [0.36; 0.71] p < 0.001 probability: “hint”	Outcome category: health-related quality of life $CI_u < 0.75$ and probability ≥ 5% lesser benefit, extent: “major”
Physical functioning	NA vs. NA HR: 1.38 [0.94; 2.04] p = 0.099	Lesser benefit/added benefit not proven
Role functioning	NA vs. NA HR: 1.48 [1.07; 2.05] HR[c]: 0.68 [0.49; 0.93] p = 0.016 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”
Emotional functioning	NA vs. NA HR: 1.29 [0.85; 1.96] p = 0.236	Lesser benefit/added benefit not proven
Cognitive functioning	20.5 vs. NA HR: 1.40 [1.03; 1.91] HR[c]: 0.71 [0.52; 0.97] p = 0.031 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”
Social functioning	NA vs. NA HR: 1.45 [1.07; 1.96] HR[c]: 0.69 [0.51; 0.93] p = 0.013 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: “minor”

(continued)

Table 16: Extent of added benefit at outcome level: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Outcome category **Outcome**	**Dacomitinib vs. gefitinib** **Median time to event (months) or MD** **Hazard ratio [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	NA vs. NA HR: 1.20 [0.84; 1.74] p = 0.321	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	5.6 vs. 23.5 HR: 1.89 [1.46; 2.45] HR[c]: 0.53 [0.41; 0.68] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and probability ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 1.31 [0.81; 2.11] p = 0.266	Greater/lesser harm not proven
Diarrhoea (PT, severe AEs with CTCAE grade ≥ 3)	NA vs. NA HR: 10.22 [2.39; 43.77] HR[c]: 0.10 [0.02; 0.42] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and probability ≥ 5% greater harm, extent: "major"
Stomatitis (PT, AEs)	NA vs. NA HR: 3.40 [2.35; 4.92] HR[c]: 0.29 [0.20; 0.43] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, severe AEs with CTCAE grade ≥ 3), including in particular dermatitis acneiform (PT)	NA vs. NA HR: 14.47 [5.82; 35.94] HR[c]: 0.07 [0.03; 0.17] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects CI_u < 0.75 and probability ≥ 5% greater harm, extent: "major"
Dry skin (PT, AEs)	NA vs. NA HR: 1.74 [1.16; 2.61] HR[c]: 0.57 [0.38; 0.86] p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe side effects 0.80 ≤ CI_u < 0.90 greater harm, extent: "minor"

(continued)

Table 16: Extent of added benefit at outcome level: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Outcome category **Outcome**	**Dacomitinib vs. gefitinib** **Median time to event (months) or MD** **Hazard ratio [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Alopecia (PT, AEs)	NA vs. NA HR: 2.02 [1.28; 3.20] HR[c]: 0.50 [0.31; 0.78] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Chest pain (PT, AEs)	NA vs. NA HR: 0.57 [0.33; 0.96] p = 0.032	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[d]
Paronychia (PT, severe AEs with CTCAE grade ≥ 3)	NA vs. NA HR: 5.82 [1.70; 19.87] HR[c]: 0.17 [0.05; 0.59] p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and probability ≥ 5% greater harm, extent: "major"
Conjunctivitis (PT, AEs)	NA vs. NA HR: 4.87 [2.44; 9.72] HR[c]: 0.21 [0.10; 0.41] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	10.2 vs. 16.3 HR: 1.33 [1.02; 1.74] HR[c]: 0.75 [0.57; 0.98] p = 0.035	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[d]
Metabolism and nutrition disorders (SOC, AEs)	15.9 vs. 25.8 HR: 1.45 [1.09; 1.93] HR[c]: 0.69 [0.52; 0.92] p = 0.011	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[d]
Back pain (PT, AEs)	NA vs. NA HR: 0.41 [0.23; 0.72] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Eye disorders (SOC, AEs)	NA vs. NA HR: 2.03 [1.21; 3.39] HR[c]: 0.49 [0.29; 0.83] p = 0.006 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"

(continued)

Table 16: Extent of added benefit at outcome level: dacomitinib vs. gefitinib (patients with the activating EGFR mutations L858R or Del19) (continued)

Outcome category **Outcome**	**Dacomitinib vs. gefitinib** **Median time to event (months) or MD** **Hazard ratio [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Investigations (SOC, severe AEs with CTCAE grade ≥ 3), including in particular alanine aminotransferase increased	NA vs. NA HR: 0.44 [0.25; 0.77] p = 0.003 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_u).
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e: Change from baseline.
f: Magnitude of the HR not interpretable (0 events in the gefitinib arm).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; L858R: substitution in exon 21; MD: mean difference; NA: not achieved; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of dacomitinib in comparison with gefitinib (patients with the activating EGFR mutations L858R or Del19)

Positive effects	**Negative effects**
Mortality: indication of an added benefit – extent: "minor" ▪ overall survival	–
–	Non-serious/non-severe symptoms/late complications: hint of lesser benefit; extent: "considerable", reflected in: ▪ diarrhoea ▪ sore mouth ▪ dysphagia ▪ neuropathy peripheral ▪ alopecia extent: "minor" ▪ appetite loss
–	Health-related quality of life: hint of lesser benefit; extent: "major" ▪ global health status extent: "minor" ▪ role functioning ▪ cognitive functioning ▪ social functioning
Serious/severe side effects: hint of lesser harm – extent: "considerable" ▪ SOC investigations (CTCAE grade ≥ 3), in particular PT alanine aminotransferase increased	Serious/severe side effects: indication of greater harm – extent: "major" ▪ SOC skin and subcutaneous tissue disorders, in particular PT dermatitis acneiform
	Serious/severe side effects: hint of greater harm – extent: "major", represented in: ▪ overall rate of severe AEs (CTCAE grade ≥ 3); ▪ specific severe AEs (CTCAE grade ≥ 3): ▫ PT diarrhoea ▫ PT paronychia
Non-serious/non-severe side effects: hint of lesser harm – extent: "considerable" ▪ PT back pain	Non-serious/non-severe side effects: hint of greater harm, represented in: ▪ PT stomatitis (extent: "considerable") ▪ PT alopecia (extent: "considerable") ▪ PT conjunctivitis (extent: "considerable") ▪ PT dry skin (extent: "minor") ▪ SOC eye disorders (extent: "minor")
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; Del19: exon 19 deletion; EGFR: epidermal growth factor receptor; L858R: substitution in exon 21; PT: Preferred Term; SOC: System Organ Class	

The overall consideration showed both positive and negative effects of dacomitinib in comparison with gefitinib. An indication of minor added benefit was shown for the outcome "overall survival", in addition to which there were individual hints of lesser harm in severe and

non-serious/non-severe side effects. On the other hand, there were numerous hints of lesser benefit or greater harm in several outcome categories, some of which of major extent.

The negative effects of dacomitinib were shown, on the one hand, in numerous side effects, particularly in severe AEs of CTCAE grade 3 and higher, and, on the other, also in earlier and/or more frequent deteriorations in patient-reported symptoms and health-related quality of life.

Overall, the large number and the large extent of the disadvantages of dacomitinib lead to the assessment that, despite mostly higher certainty of results, the positive effect for the outcome "overall survival" is outweighed by the negative effects.

In summary, an added benefit of dacomitinib versus gefitinib is not proven for adult patients in first-line treatment with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19.

This deviates from the assessment of the company, which derived an indication of a minor added benefit for this patient group.

2.3.4 List of included studies

ARCHER 1050

Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non–small-cell lung cancer and EGFR-activating mutations. J Clin Oncol 2018; 36(22): 2244-2250.

Pfizer. ARCHER 1050: a randomized, open-label, phase 3, efficacy and safety study of dacomitinib (PF 00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s): clinical trial results [online]. In: EU Clinical Trials Register. 25.10.2018 [Accessed: 20.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004977-23/results.

Pfizer. ARCHER 1050: a randomized, open-label, phase 3,efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s): study DP312804/A7471050: supplemental clinical study report [unpublished]. 2017.

Pfizer. ARCHER 1050: a randomized, open-label, phase 3, efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s): study DP312804/A7471050; additional report (interim) [unpublished]. 2017.

Pfizer. ARCHER 1050: a randomized, open-label, phase 3, efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s): study DP312804/A7471050; clinical study report [unpublished]. 2018.

Pfizer. ARCHER 1050: a randomized, open-label, phase 3, efficacy and safety study of dacomitinib (PF-00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s): study DP312804/A7471050: Zusatzanalysen [unpublished]. 2019.

SFJ LungCancer. ARCHER 1050: a randomized, open-label, phase 3, efficacy and safety study of dacomitinib (PF 00299804) versus gefitinib for the first line treatment of locally advanced or metastatic non small cell lung cancer in subjects with epidermal growth factor receptor (EGFR) activating mutation(s) [online]. In: EU Clinical Trials Register. [Accessed: 20.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004977-23.

SFJ Pharmaceuticals. ARCHER1050: a study of dacomitinib vs. gefitinib in 1st-line treatment of advanced NSCLC: study results [online]. In: ClinicalTrials.gov. 17.04.2019 [Accessed: 20.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01774721.

SFJ Pharmaceuticals. ARCHER1050: a study of dacomitinib vs. gefitinib in 1st-line treatment of advanced NSCLC: study details [online]. In: ClinicalTrials.gov. 17.04.2019 [Accessed: 20.05.2019]. URL: https://ClinicalTrials.gov/show/NCT01774721.

Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18(11): 1454-1466.

2.4 Research question 2: patients with other activating EGFR mutations

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dacomitinib (status: 20 March 2019)
- bibliographical literature search on dacomitinib (last search on 20 March 2019)
- search in trial registries for studies on dacomitinib (last search on 20 March 2019)

To check the completeness of the study pool:

- search in trial registries for studies on dacomitinib (last search on 13 May 2019)

In its dossier, the pharmaceutical company presented no relevant study on research question 2. No relevant study was identified from the check either.

2.4.2 Results on added benefit

The company presented no study on the added benefit of dacomitinib in adult patients with advanced or metastatic NSCLC with activating EGFR mutations other than L858R and Del19. This resulted in no hint of an added benefit of dacomitinib in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no data for the present research question, an added benefit of dacomitinib in this subindication is not proven.

2.4.4 List of included studies

Not applicable as the company presented no data for research question 2.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of dacomitinib in comparison with the ACT is summarized in Table 18.

Table 18: Dacomitinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC with the activating EGFR mutations L858R or Del19	Afatinib or **gefitinib** or erlotinib	Added benefit not proven[b]
Adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations other than L858R or Del19	Individual treatment depending on the activating EGFR mutation, choosing from: ▪ afatinib, gefitinib, erlotinib ▪ cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[c] ▪ carboplatin in combination with nab-paclitaxel and ▪ monotherapy with gemcitabine or vinorelbine (only for patients with ECOG PS 2 as an alternative to platinum-based combination treatment)	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The ARCHER 1050 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
c: Prescribable despite unapproved therapeutic indication; see Appendix VI to Section K of the Pharmaceutical Directive.
ACT: appropriate comparator therapy; Del19: exon 19 deletion; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; L858R: substitution in exon 21; NSCLC: non-small cell lung cancer

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-39-dacomitinib-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.12205.html.